

# Understanding the impact of breast cancer adjuvant endocrine therapy on cognitive function: a work in progress

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Breast cancer is the most common cancer in women throughout the world and is associated with extended, long-term survival as a result of the effective application of chemotherapy and endocrine adjuvant therapies (Berry *et al*, 2005; DeSantis *et al*, 2016). The majority of breast cancers are hormone receptor positive and thus endocrine therapies play a critical role in reducing the risk of both distant and local recurrence of the primary cancer (Burststein *et al*, 2014). Surgical ovarian ablation was among the earliest approaches to adjuvant therapy in premenopausal breast cancer patients; however, the success of tamoxifen in treatment of metastatic breast cancer in pre- and postmenopausal women eventually led to its introduction as the main form of endocrine adjuvant therapy in premenopausal breast cancer patients in the latter decades of the twentieth century. Since that time, a variety of investigations have asked the question of whether or not ovarian function suppression (OFS) (either with surgery or with a gonadotropin-releasing hormone agonist) added to either tamoxifen or an aromatase inhibitor would improve the durability of disease-free survival and overall survival in premenopausal women (Goel *et al*, 2009). The recently completed SOFT and TEXT trials are the most ambitious studies to date to address this question (Pagani *et al*, 2014; Francis *et al*, 2015).

While improved survival is a central goal of adjuvant endocrine therapy, one must have respect for both the short-term and long-term complications of these treatments, especially in younger women, who are likely to have extended years of survival (Zwart *et al*, 2015). The short-term side effects of endocrine therapy include vasomotor, vaginal and sexual difficulties, with musculoskeletal complaints being more frequent with aromatase inhibitors (Bernhard *et al*, 2015; Ganz *et al*, 2016). Long-term risks include diminished bone density/fracture, thromboembolic events, uterine cancer, and potentially increased cardiac disease (Burststein *et al*, 2014). Until recently there has been limited examination of the potential for cognitive difficulties associated with initiation of

endocrine adjuvant therapy (Bender *et al*, 2007, 2015; Buwalda & Schagen, 2013; Ganz *et al*, 2014; Boele *et al*, 2015), as most earlier attention has focused on the potential for cognitive decline in association with chemotherapy (Ahles *et al*, 2012; Wefel *et al*, 2015).

There is emerging evidence that endocrine therapy in breast cancer patients is associated with cognitive difficulties, which is not surprising given the critical role of oestrogens in maintaining neural plasticity (Buwalda and Schagen, 2013). Numerous studies in healthy women demonstrate diminished verbal memory and verbal fluency in association with surgical or medical ovarian suppression (Zwart *et al*, 2015), as well as increased risk for dementia with premature menopause (Rocca *et al*, 2011, 2014). Decline in these same domains of neurocognitive function has also been noted in association with tamoxifen therapy (Boele *et al*, 2015). In their recent review, Zwart *et al* (2015) note that most studies of cognitive function in association with endocrine treatment of breast cancer have been small observational studies, and they call for more comprehensive assessments of the impact of this therapy on cognition. They also emphasise the importance of obtaining cognitive function assessments in clinical trials, as well as the critical need for long-term follow-up, as women with breast cancer are expected to have extended survival times in which cognitive decline might emerge as an important late consequence of treatment.

With this background, we need to consider the strengths and limitations of the report by Phillips *et al* (2016) in this issue of the *British Journal of Cancer*, describing an evaluation of cognitive function in women participating in the SOFT trial. The Co-SOFT substudy had an initial planned enrollment goal of 321 SOFT study participants who would be recruited at one of the 26 sites that were participating in the SOFT trial. The planned primary outcome for Co-SOFT was a comparison of objective cognitive function before the initiation of endocrine therapy and then 1 year later, across the

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three separate SOFT trial treatment groups. Additional questionnaires were administered to assess self-reported cognitive function, psychological distress, fatigue, insomnia and quality of life. Overall, this was a well-designed and comprehensive approach to assessing cognitive function/decline as part of an important randomised clinical trial.

Unfortunately, due to low accrual at the substudy participating centres and early closure of the parent trial, the sample recruited for Co-SOFT was substantially smaller than expected. The protocol was then revised to compare the tamoxifen sample to the combined OFS arms of the study, and we are told that the observed sample size (86 enrolled and 74 evaluable, in a two-group design) provided 80% power to detect an effect size of 0.76 with a two-sided  $\alpha = 0.05$ . This is a large effect size for comparison of two endocrine therapies with overlapping toxicities and mechanisms of action. The authors do not report the original effect size that the study had been planned to detect, and it is likely that it was much smaller. Thus, the comparison presented in this analysis is underpowered to detect a likely difference of a small to medium effect between tamoxifen alone and the two OFS groups.

Additional concerns about the current report include the fact that while patients were randomly assigned to the three SOFT trial arms before being approached for Co-SOFT, the substudy inclusion required that patients could not have initiated endocrine therapy prior to randomisation (true for ~70% of patients enrolled during the period of recruitment). However, use of endocrine therapy prior to randomisation was not a trial stratification factor, and thus those who were eligible for the Co-SOFT study may not have been randomly allocated. Further undermining the likelihood that the final Co-SOFT sample reflects the trial random assignments is the fact that only 86 of 102 eligible patients joined the substudy during the recruitment period, and only 74 were assessed at two time points (before treatment and 1 year later). Thus, the treatment arms compared in this report reflect an observational cohort study design, with the sample being drawn from the parent SOFT trial.

The primary comparison in Co-SOFT was the change in the Composite Score of the CogState tasks, which was the measure used to assess neurocognitive function. Unfortunately, this test battery omitted the verbal fluency domain that is often affected by changes in oestradiol levels. Furthermore, a global composite score might not be as sensitive an indicator of cognitive dysfunction in this setting, since patients who experience cognitive changes with cancer therapy rarely exhibit global impairments, and have more often been noted to have subtle deficits in specific neurocognitive domains, such as verbal and visual memory, along with processing speed (Wefel *et al.*, 2015). Although self-reported cognitive complaints were a secondary outcome in this study, the patients receiving OFS reported a substantially greater perceived decline in functioning compared to the tamoxifen-alone group. While the CogState composite score did not correlate with the self-reported functioning, in a recent study we found that women who initiated endocrine therapy for breast cancer with either tamoxifen or an aromatase inhibitor had worse performance on a cognitive assessment of psychomotor speed, and this was associated with specific aspects of verbal fluency (Ganz *et al.*, 2014). The small sample size in the Co-SOFT study, as well as the focus on global assessment of cognitive function, likely limited the ability to detect true objective neurocognitive deficits associated with the use of OFS.

Nevertheless, Phillips *et al.* should be congratulated for the effort they made to coordinate a comprehensive cognitive function assessment study within this important international adjuvant treatment trial. As with many ancillary studies, they are often difficult to conduct because of a lack of resources, and as a result their initiation is delayed and accrual may be limited. Future studies of cognitive decline must incorporate evaluations from

inception of the trial so that adequate sample size and power are present to determine whether or not cancer treatments impact cognitive function. In particular, if self-reported cognitive function can reliably detect treatment-associated impairments, then this may be a more efficient way to universally assess cancer treatment-related cognitive impairment in the setting of randomised clinical trials.

## CONFLICT OF INTEREST

Dr Ganz was an investigator participating in the SOFT trial.

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